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Original Article

Inflammation and host-pathogen interaction: Cause and consequence in cystic fibrosis lung disease

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Abstract

Cystic Fibrosis (CF) lung disease is associated with dysregulation of host defence systems, which ultimately disrupts the balance between inflammation and resolution and leaves the host susceptible to repeated infection. However, the mechanisms underlying these defects are complex and continue to garner significant interest among the CF research community. This review explores emerging data on novel aspects of innate host defence with promising biomarker and therapeutic potential for CF lung disease. Improved understanding of inflammation and host defence against pathogens in patients and animal models during the progression of CF lung disease is pivotal for the discovery of new therapeutics that can limit and/or prevent damage from birth.

Keywords: Lung; Host defence; Inflammation; Animal models; Infection; Cystic fibrosis

1. Introduction

Inflammation and tissue remodelling are major aspects of cystic fibrosis (CF) lung disease and have long been the focus of many CF researchers searching for an effective therapeutic strategy to prevent and repair CF-associated lung damage, which is evident even in young children with CF [1–3]. Chronic bacterial infections undoubtedly play a prominent role in the progression of CF lung disease. However, evidence of inflammatory lung disease is observed by Computerized Tomography (CT) scan analysis in asymptomatic CF infants, without apparent established bacterial infection [4], suggesting that sterile inflammation can precede and possibly facilitate subsequent infection in early stage CF lung disease. Work is ongoing to identify key drivers of this early inflammation and its role in the pathogenesis and progression of CF lung disease.

Animal models have shed some light although data are not conclusive and further evaluation of the immunophenotypes of the CF lung is required. In unchallenged CFTR- deficient mice, enhanced myeloid infiltration and dendritic cell polarization was recently observed [5], as well as abnormal macrophage phenotype [6] and increased inflammatory responses to challenge [7], suggesting a state of inflammation in the absence of pathogens. In the *Scnn1b*-Tg mouse model, recent studies indicate that airway mucus obstruction may be a potent trigger of chronic airway inflammation and associated lung damage, independent of bacterial infection [8]. The lungs of CF ferrets do not display lung infections when treated with antibiotics from birth, but do show neutrophil dominated inflammation and bronchiectasis [9]. However, although CF pigs lacked detectable pulmonary inflammation at birth, large airway remodelling was evident and the lungs from CF pigs were less sterile and had higher bacterial counts suggesting that infection may precede inflammation in this model

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[10]. While most of the studies in animal models are focused to the early phases of the disease, long-term chronic infection remains less investigated. Recently, a murine model in which *Pseudomonas aeruginosa* infection demonstrated that *P. aeruginosa* persistence led to CF hallmarks of airway remodelling and fibrosis [11].

In this targeted review, we explore emerging facets of inflammation and host defence that may play a role in the pathogenesis of early CF lung disease. The role of bioactive lipids and the cysteine protease cathepsin S (CTSS) as markers of CF lung disease but also as agonists driving inflammatory lung disease is discussed. In addition, findings on the use of novel animal models of CF lung disease and infection are described, and we highlight how these may be used to generate information that is relevant to human disease. Readers are directed to a number of recent reviews, that outline current and emerging aspects of myeloid cell dysfunction and inflammation, which are beyond the scope of this review [3,12–15].

2. Bioactive lipids as markers and agonists in CF lung disease

Several lines of evidence point towards a role of bioactive, i.e. receptor activating, lipids in CF lung disease. Spontaneous lung inflammation in F508del CFTR mice (*Cftr*^{tm1EUR}), characterized by enhanced infiltration with granulocytes and monocyte derived dendritic cells, correlates with reduced lung sphingosine-1-phosphate (S1P) levels. This could be partially corrected with an inhibitor of S1P ligase [5], suggesting that unbalanced S1P metabolism is a consequence of CFTR deficiency in the lung, and contributes to sterile inflammation through modulation of receptors of the S1PRn family. Since experimental anti-inflammatory drugs have been developed targeting S1P metabolism and its receptors [16], therapeutic intervention in CF lung disease can be considered an option, though further research is required to establish safety and efficacy. In addition, cellular phospholipase A (cPLA2) activity is enhanced in CFTR deficient epithelia, affecting the production of arachidonic acid, and downstream inflammation agonists (lysolipids, prostaglandins), and cPLA2 inhibition reduced mucus production in CF mice [17]. Several experimental drugs targeting the PLA family are in trial for the treatment of inflammatory disease and cancer [18], but none have reached the clinical market so far [19]. Changes in ceramide synthase activity, increasing the long chain (LCC) to very long chain ceramide ratio (VLCC) in the CF mouse lung and human CF plasma have been recently observed. Treatment with the retinoic acid analogue fenretinide corrects this abnormality, and reduces inflammation in mutant mice and shows efficacy in a phase 1 clinical trial [20]. A change in ceramide chain length likely changes the activity and cross-talk of key regulating receptors and kinases, contributing to unbalanced inflammatory responses in CF lung. Together, these data suggest that the abnormal bioactive lipid levels involved are not merely markers of inflammation but are a direct consequence of CFTR deficiency and play an active part in the progression of CF lung disease.

To further establish the role of bioactive lipids in early CF disease, a comprehensive mass spectrometry lipidomics analysis of bronchial lavage fluid (BALF) from infants (1–6 year), provided by the Australian AREST CF consortium (represented by Dr. Stephen Stick, University of Western Australia, Perth, Australia) and the ErasmusMC I-BALL team (represented by Dr. Hettie Janssens, Erasmus MC, Rotterdam, The Netherlands) was recently completed. CF patients ($N = 60$) were compared to age matched non-CF patients ($N = 20$), with comparable levels of inflammation. A detailed report is outside the scope of this review and will be published elsewhere. In particular, an increase of long chain ceramides (Cer18:1/16:0) compared to very long chain (Cer18:1/24:0) was observed in CF infants with a high bronchiectasis score compared to non-CF. This confirms and extends in CF infants with early stage lung disease the study of Radzioch et al. [20]. Further, lysolipids were high in CF BALF and correlated with inflammatory markers (IL-8, % neutrophils) and lung CT scores. This suggests that the druggable PLA pathway also plays a role in the progression of CF lung disease, by enhancing the epithelial production of pro-inflammatory cytokines and thus myeloid infiltration through the lysolipid receptors (LPAn) receptors [21]. Lipid markers associated with oxidative stress (isoprostanes) distinguish patients with high and low CT scores, suggesting that this is a CFTR related factor in the progression of lung disease and a potential therapeutic target. Future studies are aimed at elucidating the molecular mechanisms that couple CFTR dependent oxidative stress and pro-inflammatory lipid signalling, in advanced cell culture models. A tentative model is presented in Fig. 1, proposing that enhanced oxidative stress, at least in part caused by deficient glutathione transport [22,23], affects downstream lipid metabolism and subsequently pro-inflammatory signalling, neutrophil transmigration and activation, and finally host pathogen interactions.

3. Cathepsin S in the pathogenesis of CF lung disease

Proteases, in particular the serine protease neutrophil elastase (NE), are traditionally recognised as key mediators of the damage in the CF lung, however, previous approaches targeting protease neutralisation in the CF lung have had limited success. Recent work suggests that other host proteases may play an important role in the pathogenesis of CF lung disease. One such protease is the cysteine protease cathepsin S (CTSS) which was first detected in CF lung secretions in 2003 [24]. Since then, pulmonary CTSS (antigenic levels and/or proteolytic activity) has also been shown to correlate with a number of biomarkers of CF lung disease, such as a decline in lung function (FEV1% predicted) and pulmonary neutrophilia in early CF [25], as well as TNF-α and IL-8 in adult CF patients [26]. In paediatric patients with CF, CTSS was significantly increased in *Pseudomonas*-negative preschool children with CF compared to children without CF with recurrent respiratory infection, suggesting that this may be related to CFTR dysfunction [25]. Cellular sources of pulmonary CTSS include airway epithelial cells via dysregulated miR-31/IRF-1 signalling in CF epithelium [25], however macrophages and neutrophils [27,28] also represent potential sources in the CF lung.

In agreement with previous work, no difference was detected between *Pseudomonas*-positive and *Pseudomonas*-negative CF

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